DETAILED ACTION

Status of the Claims

1. Claims 8-10, 12, 14-19, 32-35, 39, 40 and 44-53 are pending.

Applicants' amendment filed on January 14, 2009 is acknowledged. Applicants' response has been fully considered. Claims 8, 46 and 48 have been amended. Thus, claims 8-10, 12, 14-19, 32-35, 39, 40 and 44-53 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claims 8-10, 14-19, 46, 48 and 50 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claims, and applicant's response at pages 17-18 of the amendment filed January 14, 2009.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mark Moore on March 25, 2009.

Examiner's Amendment to the Specification:

Please replace the term "Scheme 8" at page 68, line 3 with the term "Scheme 10".

Please replace the term "Experimental to Example 10" at page 91, line 27 with the term "Experimental to Example 9".

Please replace the term "Experimental to Example 11" at page 106, line 6 with the term "Experimental to Example 10".

Examiner's Amendment to the Claims:

Cancel claims 15 and 18.

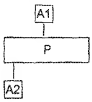
Claims 8, 17, 32, 33, 46, 48 and 53 have been amended as follows:

8. (Currently amended) A method of ~~synthesis of~~ synthesizing a cyclic peptide or peptidomimetic compound of General Formula I

General Formula I

in which the cycle is a monocycle, bicycle or higher order cyclic peptide or peptidomimetic compound comprising 2 to 15 monomers, which is carried out in solution, comprising the steps of:

a) preparing a linear peptide or peptidomimetic compound of General Formula III



General Formula III

where **P** is a linear peptide or peptidomimetic compound of 2 to 15 monomers, **A1** and **A2** are substituents on **P**;

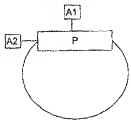
A1 is one or more reversible N-substituents, on the peptide backbone, or is a chemical moiety that forces a cis conformation of the backbone, and

A2 is a covalently-bonded group of atoms comprising a reactive functionality to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide;

b) activating the C-terminus to form a cyclic peptide or peptidomimetic compound of General Formula IV~~:~~;

General Formula IV

c) ~~Permitting~~ permitting the peptide or peptidomimetic compound of General Formula IV to rearrange via a ring contraction reaction to form a cyclic peptide or peptidomimetic compound of General Formula V; and



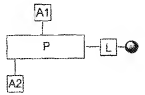
General Formula V

d) ~~Subjecting~~ subjecting the cyclic peptide or peptidomimetic compound of General Formula V to a deprotection reaction to remove the **A1** and **A2** groups to yield the desired cyclic peptide or peptidomimetic compound of General Formula I ~~or General Formula II~~.

17. (Currently amended) The method of claim 16, in which **A2** ~~is~~ comprises thiol or hydroxyl.

32. (Currently amended) A method of performing solid phase synthesis of a cyclic peptide, comprising the steps of:

a) ~~synthesis of~~ synthesizing a linear solid support-bound peptide of General Formula XIII,



General Formula XIII

where **P** is a linear peptide of 2 to 15 monomers, **A1** and **A2** are substituents on **P**;
A1 is one or more N-substituents, either reversible or non-reversible, on the peptide backbone, or is a chemical moiety that forces a cis conformation of the backbone, and
A2 is a covalently-bonded group of atoms comprising a reactive functionality to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide; and
L is a linker between any atom of the peptide and the solid support; ~~and~~

b) subjecting the peptide of General Formula XIII to cyclization and concomitant cleavage from the solid support to yield a cyclic peptide of General Formula XIV,

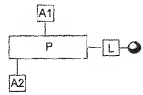
General Formula XIV

c) subjecting the cyclic peptide of General Formula XIV to ring contraction, and

d) if **A1** is a reversible substituent, cleaving the groups **A1** and **A2** to yield the desired cyclic peptide of General Formula I:

33. (Currently amended) A method of performing solid phase synthesis of a cyclic peptide, comprising the steps of;

a) ~~synthesis of~~ synthesizing a linear solid support-bound peptide of General Formula XIII,



General Formula XIII

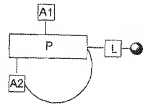
where **P** is a linear peptide of 2 to 15 monomers, **A1** and **A2** are substituents on **P**;

A1 is one or more N-substituents, either reversible or non-reversible, on the peptide backbone, or is a chemical moiety that forces a cis conformation of the backbone, and

A2 is a covalently-bonded group of atoms comprising a reactive functionality to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide; and

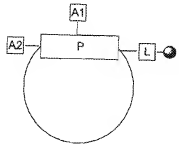
L is a linker between any atom of the peptide and the solid support; ~~and~~

b) subjecting the linear peptide to cyclization on the solid support to yield a cyclic peptide of General Formula XV,



General Formula XV

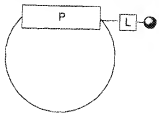
c) subjecting the cyclic peptide to ring contraction to yield a cyclic peptide of General Formula XVI,



General Formula XVI

and either

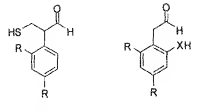
d) cleaving groups **A1** and **A2** while the peptide is bound to the solid support to yield a resin-bound cyclic peptide of General Formula II, or



General Formula II

e) subjecting the cyclic peptide to deprotection and concomitant cleavage from the solid support to yield the desired cyclic peptide of General Formula I:

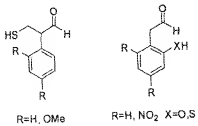
46. (Currently Amended) The method of claim 32, in which **A2** is formed by reacting an amine nitrogen in **P** with a compound selected from the group consisting of:



and

wherein ~~said auxiliary~~ **A2** facilitates contraction of said ring to form said cyclic peptide.

48. (Currently Amended) The method of claim 33, in which **A2** is formed by reacting an amine nitrogen in **P** with a compound selected from the group consisting of:

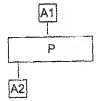


and

wherein ~~said auxiliary~~ **A2** facilitates contraction of said ring to form said cyclic peptide.

53. (Currently amended) A method of ~~synthesis of~~ synthesizing a cyclic peptide or peptidomimetic compound, which is carried out in solution, comprising the steps of:

a) preparing a linear peptide or peptidomimetic compound of General Formula III



General Formula III

where **P** is a linear peptide or peptidomimetic compound of 2 to 15 monomers, **A1** and **A2** are substituents on **P**;

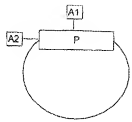
A1 is one or more N-substituents, either reversible or non-reversible, on the peptide backbone, or is a chemical moiety that forces a cis conformation of the backbone, and

A2 is a covalently-bonded group of atoms comprising a reactive functionality to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide;

b) activating the C-terminus to form a cyclic peptide or peptidomimetic compound of General Formula IV:

General Formula IV

c) permitting the peptide or peptidomimetic compound of General Formula IV to rearrange via a ring contraction reaction to form a cyclic peptide or peptidomimetic compound of General Formula V; ~~and~~



General Formula V

d) wherein either the **A1** group or the **A2** group is left attached to the peptide, or both **A1** and **A2** are left attached to the peptide.

The following is an Examiner's Statement of Reasons for Allowance: The following references are related to the claimed invention. Ehrlich *et al.* (J. Org. Chem. 61, 8831-8838 (1996)) disclose reversible amide bond alkylation such as Hmb (2-hydroxy-4-methoxyl benzyl)-modification on the peptide promotes the cyclization of peptides devoid of turn-inducing amino acid residues. Beusen *et al.* (Biopolymers 36(2) 181-260 (1995)) teach a cis amide bond surrogate, 1,5-disubstituted tetrazole was placed into peptides for synthesizing hexapeptie analogs of somatostatin. Elseviers *et al.* (Biochem. Biophys. Res. Comm. 154 (2), 515-521 (1988)) teach N-methyl-α-benzyl-o-aminomethylphenylacetic acid was incorporated into a cyclic somatostatin analog in order to mimic a cis-peptide bond configuration. Botti *et al.* (J. Am. Chem. Soc. 118 10018-10024 (1996)) teach a general method for the preparation of cyclic peptide by intramolecular thiazolidine formation from linear, unprotected peptide precursors, which contain a protected 1,2-aminothiol from N-terminal cysteine and a 1,2-aminoalcohol or 1,2-diol as masked aldehyde, where high efficiency of macrocyclization may be attributed to the ring-chain tautomerism of the open chain amino-aldehyde precursor that favors of a macrocyclic thiazolidine ring. However, these references do not teach or suggest the use of two substituents on the peptide to facilitate the formation of a cyclic peptide, where the two substituents are: (a) an N-substituent on the peptide backbone or a chemical moiety that forces a cis conformation of the backbone and (b) an auxiliary substituent that facilitates the formation of initial large cyclic peptide prior to ring contraction to the desired cyclic peptide. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
March 26, 2009